Do Sunscreens Increase or Decrease Melanoma Risk: An Epidemiologic Evaluation

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Ultraviolet adiation is an important cause of melanoma, so the use of sunscreen lotions has been advocated for melanoma prevention. Several arguments have been raised in opposition to this inference. Sunscreen use may interfere with cutaneous vitamin D synthesis, which some have hypothesized may lower melanoma risk. Sunscreen users may compensate for their sunscreen use by staying out much longer in the sun, or may use sunscreen lotions inconsistantly. Published melanoma case-control studies have not consistantly demonstrated a protective effect of sunscreens; however, these studies do not provide strong evidence, ultraviolet radiation is a known cause of melanoma, and ultraviolet B may be particularly potent, so on balance the evidence supports continued advocacy of sunscreen lotion use as part of an overall sun-protection regimen. Uncertainty will remain, however, until the action spectrum of melanoma is convincingly demonstrated or the methodologic limitations of existing epidemiologic evidence are overcome. The latter may require another decade or more of experience with sunscreen use. *Key words: case-control studies/epidemiology/melanoma/sunscreen. Journal of Investigative Dermatology Symposium Proceedings 4:97–100, 1999*

It is now well-established that ultraviolet radiation from the sun is a causal factor in the etiology of melanoma (International Agency for Research on Cancer, 1992). This conclusion, and the extensive body of evidence supporting it, have not been subject to serious challenge. The use of sunscreen lotions to prevent melanoma, however, although widely recommended, has been the subject of some controversy (Angier, 1990; Garland *et al*, 1993; Naylor *et al*, 1995; Weinstock, 1997; Gasparro *et al*, 1998).

VITAMIN D

Concern has been expressed that vitamin D may inhibit melanoma formation, and that sunscreen use may lead to decreased levels of vitamin D, and therefore to greater risk of melanoma (Angier, 1990; Garland *et al*, 1993). The human body obtains vitamin D from two major sources: synthesis in the skin using ambient ultraviolet radiation and ingestion in the diet. If ultraviolet-induced vitamin D inhibits melanoma, so should the chemically identical diet-derived vitamin D. Indeed, dietary vitamin D assessed by questionnaire has been correlated with vitamin D stores even in summer months (Sowers *et al*, 1986). Hence a case-control study was performed to evaluate the association of dietary vitamin D with melanoma risk (Weinstock *et al*, 1992).

The study population included Caucasian adult outpatients who had no personal history of noncutaneous malignancy, no medical diagnosis that could affect nutritional status, and no history of metastatic skin cancer. Cases included 165 melanoma patients, and controls included 209 patients with neither melanoma nor dysplastic nevi. Dietary intake was assessed by a previously validated food frequency questionnaire, and adjusted for total energy intake (Willett *et al*, 1985; Stryker *et al*, 1990). The mean adjusted vitamin D intake (±SE), including supplements, in cases and controls was 347 ± 25 IU and 309 ± 19 IU, respectively ($p = 0.2$). Similarly, there were no significant differences if supplements were excluded, and supplements themselves were associated with an odds ratio of 1.3 (95% confidence interval 0.8–2.2, $p = 0.3$), where an odds ratio significantly less than 1.0 would have suggested that melanoma risk is associated with decreased vitamin D intake. Furthermore, the leading source of vitamin D from food, i.e. milk consumption, was also not associated with melanoma risk in this study. The relation of melanoma risk to vitamin D ingestion by quintile of total dietary vitamin D intake is displayed in **Table I**. No significant trend was noted. These data suggest that vitamin D intake is unrelated to melanoma risk. To the author's knowledge, no substantial contradictory evidence has been published (Weinstock *et al*, 1992).

Other arguments have also been forwarded against the vitamin D–melanoma link, including the tight metabolic regulation of levels of the active form of vitamin D in patients who are not frankly vitamin D deficient. Also, clinical trials of sunscreen use have not produced abnormally low vitamin D levels, and extraordinarily photoprotected populations have been noted to have normal vitamin D levels (Marks *et al*, 1995; Sollitto *et al*, 1997).

ACTION SPECTRUM

The action spectrum for erythema in humans has been determined (McKinlay and Diffey, 1987). The Sun Protection Factor (SPF) number on the label of sunscreen lotions is based on the erythema reaction in humans, and many of the sunscreen products sold are very effective in preventing erythema, as indicated by an SPF number of 15 or greater. Unfortunately, the animal models available for melanoma are quite limited, and the action spectrum for melanoma itself is unknown. The rare genetic disorder xeroderma pigmentosum may serve as a model for melanoma in the general population (Weinstock, 1992). Individuals with this disorder have an inherited defect in the repair of UVB-induced pyrimidine dimers in their DNA, which is associated with a markedly increased susceptibility to sunburn and a several thousand-fold greater risk of melanoma than the general population, despite a

Manuscript received December 10, 1998; revised March 23, 1999; accepted for publication March 25, 1999.

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Table I. Relation of vitamin D intake to melanoma risk (Weinstock *et al*, 1992)

Quintile of vitamin D intake[a]	Relative risk	95% confidence interval
<105 IU	1.0	reference group
106–188 IU	1.0	0.5–2.1
189–266 IU	0.7	0.3–1.5
267–394 IU	1.3	0.6–2.6
>395 IU	1.8	0.9–3.5

[a]Calorie-adjusted daily intake, controlled for age, hair color, and family history of melanoma.

similar distribution of melanomas on the body surface (Kraemer *et al*, 1994). This observation is consistant with the hypothesis that the action spectrum for melanoma is similar to the erythema action spectrum.

Nevertheless, additional models are needed before inferences can be drawn with confidence. Present evidence is insufficient to exclude the possibility that the melanoma action spectrum is more heavily weighted in the UVA region than the erythema action spectrum. This possibility gives rise to another possible mechanism by which melanoma risk could be augmented by sunscreen use.

THE COMPENSATION HYPOTHESIS

The compensation hypothesis posits the following: (i) sunscreens are more effective at blocking the erythema action spectrum than the melanoma action spectrum; (ii) people who use sunscreen use it primarily to avoid sunburn; (iii) hence people will increase their sun exposure substantially due to application of sunscreen lotions, to the point at which they get their usual degree of sunburn; (iv) sunscreen users will thereby actually expose themselves to more solar radiation in the wavelengths responsible for melanoma induction, and hence develop more melanomas.

Premise (i) depends on there being a substantial difference between the action spectra for erythema and the one for melanoma, which has certainly not been demonstrated. Even if it is true, the compensation hypothesis depends on the difference being of substantial enough magnitude to overcome the protection afforded by sunscreens against the melanomagenic wavelengths of solar radiation. Proponents of this premise typically argue that UVA is primarily responsible for melanoma, whereas UVB is primarily responsible for sunburn. It is true that most sunscreen lotions are relatively more effective at blocking UVB than UVA, although some increasingly popular components of sunscreens, e.g. titanium dioxide and zinc oxide, block well into the UVA range.

Premise (ii), that sunscreens are used primarily to avoid sunburn, is certainly not true for some, and is likely untrue for a substantial segment of the population, although good population-based data are lacking. One study of 200 randomly selected 13–14-y-old adolescents in Marseille in 1989 found that 15% used sunscreens to prevent long-term complications, 60% to avoid sunburns, but only 6% to allow greater sun exposure (Grob *et al*, 1993). Those who use sunscreen for melanoma prevention are, by definition, not using them primarily for sunburn avoidance, so if public health campaigns for cancer prevention are at all effective in persuading the population to use sunscreens, they are likely to be effective in persuading them to use them for reasons other than sunburn avoidance. Conclusion (iii), that sunscreen users compensate for the sunscreen use by staying in the sun longer to achieve their usual degree of sunburn, is therefore questionable. In our own surveys of beachgoers in south-eastern New England, there was a positive correlation between the use of sunscreen and the use of other sun protection techniques, such as wearing a shirt and limiting time in the sun (Weinstock and Rossi, 1998; Weinstock *et al*, 1998). Furthermore, in many situations, one simply cannot achieve a sunburn while wearing sunscreen. For example, a New Englander who may develop a painful sunburn after an hour on the beach at noon in the summer without sunscreen would find it impossible to burn with a proper application of an SPF 15 sunscreen, because there is simply not enough ultraviolet radiation reaching New England beaches between dawn and dusk, even in the summer. In temperate climates where much of the population lives, sunscreen users cannot fully compensate (i.e. to the point of burning). The limited degree of compensation that is possible for many limits more severely the possibility of increasing exposure to wavelengths of radiation potentially more effective in melanoma induction. Hence the conclusion (iv) of the compensation hypothesis is likely to be incorrect, and is particularly likely to be incorrect for much of the U.S.A. population that lives in areas (such as New England) with modest ultraviolet flux.

INCONSISTENT USE

Melanoma risk has been linked with intense intermittent exposure to solar radiation (Elwood, 1992; Elwood and Jopson, 1997). Sunscreens could therefore theoretically increase melanoma risk if they led to increased intermittency of ultraviolet radiation exposure. Of course, intermittent use is not recommended by manufacturers or public health campaigns; indeed, quite the contrary. Nevertheless, some individuals may use sunscreens irregularly when exposed to intense solar ultraviolet. If these individuals were already exposing themselves intermittently to solar radiation, inconsistent sunscreen use would not affect the "intermittentcy" of their exposure, but would reduce the magnitude of their exposure. On the other hand, if these people were constantly exposed to intense sunlight, and used sunscreens inconsistently, that would result in a more intermittent exposure pattern and hence, possibly greater melanoma risk. Furthermore, even people who apply sunscreen lotions consistently when in intense solar radiation may occasionally miss a spot, which then becomes an intermittently exposed location.

CASE-CONTROL STUDIES

To date 12 epidemiologic studies of the relation of sunscreen use to melanoma risk have been published, and one additional unpublished study is known to this author (Berwick *et al* unpublished data). In three of these, sunscreen use was associated with decreased melanoma risk (although assessment of statistical significance was unavailable for one), in four, with increased risk, and in six no clear association was demonstrated (see **Table II**). The apparently descrepant results underscore the importance of several methodologic issues.

The first group of issues relate to the characterization of the sunscreen lotions used. These studies usually failed to distinguish between lotions with low SPF values and those with high SPF values (the exceptions are listed in **Table II**), whether the general term used in the questions referred to "sun lotions", "sunscreens', or "suntan lotions". None of these studies reported their data within strata of SPF (although one shared this unpublished data; Green *et al*, 1986), so we generally do not know the proportion of users who applied SPF 2 lotions and the proportion who applied lotions with SPF greater than 15. The SPF number may not have been printed on the bottle label during the years that some of these study participants were using these lotions.

In Europe, but not in the U.S.A., some sunscreen lotions contain 5-methoxypsoralen (5-MOP). This is a close relative of 8-methoxy-psoralen, which has been linked to melanoma induction in human psoriasis patients in a recent study (Stern *et al*, 1997). Hence it becomes critical to determine whether the lotions used by study participants contained this ingredient. Only one study (Autier *et al*, 1995) separated these two types of lotions in their analysis.

The initiation, duration, frequency, circumstances, and consistency of sunscreen use are particularly important in evaluating a potential link to melanoma risk. Crude assessment of frequency of application, and in some cases duration of use, were included in many of the studies, but the level of detail was, in general, quite limited.

Exposure assessment is also complicated by the limitations of retrospective recall, and by the possibility of recall bias, which has been demonstrated for some melanoma risk factors (Weinstock *et al*, 1991).

The second group of issues pertains to the analysis of results. Although some of the reports did describe detailed analyses, most did not because these analyses were not central to their manuscripts. Of particular interest is the dose–response relation with consistancy of use, duration of use, time since initiation of use, SPF of the lotions used, and frequency of use. Adjustment for a presumed lag time between

Table II. Case-control studies of the association of sunscreen use and melanoma risk

Study	Relative risk (95% CI)	Year	Location	Control vars[a]	Reference
United States					
Graham	2.2 (1.2–4.1) men 1.7 (1.1–2.7) men (suntan lotions) ns women	1974–80	New York State	none	(Graham *et al*, 1985)
Herzfeld	ns	1977–79	New York State	ss, se	(Herzfeld *et al*, 1993)
Berwick	1.1 (0.8–1.5) sometimes 1.3 (0.9–1.6) almost always	1987–89	Connecticut	ss, se	(unpublished data 1998)
Holly	0.7 (0.5–0.9) sometimes 0.5 (0.3–0.7) never	1981–86	California	ss, sunburns	(Holly *et al*, 1995)
Australia					
Green	0.8 always when in sun (0.6 high SPF, 0.8 low SPF, 2.5 tanning oils)	1979–80	Queensland	ss	(Green *et al*, 1986) and (unpublished data 1998)
Holman	1.1 (0.7–1.6) $<$ 10 y use 1.2 (0.8–1.7) $>$ 10 y use 1.1 (0.7–1.7) $<\frac{1}{2}$ time 1.1 (0.8–1.6) $>\frac{1}{2}$ time	1980–82	Western Australia	ss	(Holman *et al*, 1986)
Whiteman	Use on holiday (*versus* never/rarely) 1.5 (0.3–8.2) sometimes 1.5 (0.3–7.4) often 2.2 (0.4–11.6) always Use at school (*versus* never/rarely) 0.8 (0.3–2.1) sometimes 1.6 (0.5–5.5) often 0.7 (0.1–6.0) always	1987–94	Queensland[b]	ss, freckling	(Whiteman *et al*, 1997)
Europe					
Klepp	1.8 (1.2–2.7) sometimes/quite often 3.1 (1.4–7.1) almost always	1974–75	Norway	none	(Klepp *and* Magnus, 1979)
Beitner	1.6 (1.1–2.3) seldom 1.7 (1.0–2.9) often/very often	1978–83	Sweden	ss	(Beitner *et al*, 1990)
Osterlind	1.3 (1.0–1.6) occasionally 1.1 (0.8–1.5) always 1.3 (0.9–1.7) $<$ 10 y 1.2 (0.9–1.5) 10+ y	1982–85	Denmark	none	(Osterlind *et al*, 1988)
Westerdahl	1.3 (0.9–1.9) sometimes 1.8 (1.1–2.8) almost always	1988–90	Sweden	ss, se	(Westerdahl *et al*, 1995)
Rodenas	0.6 (0.3–1.4) sometimes 0.2 (0.0–0.8) always	1989–93	Spain	ss,se	(Ródenas *et al*, 1996)
Autier	1.5 (1.1–2.1) without 5-MOP 2.3 (1.3–4.0) with 5-MOP 1.3 (0.8–2.1) self-tanning cosmetics	1991–92	Germany, France, Belgium	ss, se	(Autier *et al*, 1995)

[a] Report included analyses controlled for an indicator of sun sensitivity (ss) or sun exposure (se) if indicated. Some reports included analyses controlled for other variables as well (e.g., gender). None included control for socioeconomic status.
[b] All cases age 0–14 y.

exposure to ultraviolet radiation and diagnosis of melanoma also would be useful.

Confounding is a particular concern in this group of studies. In particular, sun sensitivity, sun exposure, and socioeconomic status are all likely to be confounding variables, because each of these are associated with both sunscreen use and melanoma risk. Manifestations of sun damage may also lead to sunscreen use. As indicated in **Table II**, some of these variables were controlled in many of the reports. Any one of them could produce a spurious association between sunscreen use and melanoma risk, and indeed, two of the reports (Holman *et al*, 1986; Herzfeld *et al*, 1993) noted that crude associations disappeared after adjustment. It should be noted that appropriate adjustment for these variables, particularly sun exposure, is quite difficult because sun exposure in particular is a difficult variable to measure accurately with retrospective recall. Hence even after adjusting for confounders, the possibility of residual confounding must be considered.

Publication bias is an important concern in evaluating the sunscreen-melanoma link because negative findings may be viewed as unattractive to journal editors and hence be less likely to be submitted for publication and less likely to be published. In addition, negative findings have in general been presented in much less detail when published. Similarly, observations that sunscreens protect against melanoma may be de-emphasized because that is the conventional expectation, and observations that sunscreens are risk factors for melanoma may be withheld because they are presumed artifacts of methodologic defects, such as those discussed herein.

Finally, statistical power is an absolutely critical issue. Sunscreening lotions with SPF $>$ 5 did not exceed lotions with SPF $<$ 5 in sales in the U.S.A. until 1987. Hence most of the pre-1987 use of sunscreens was of relatively ineffective products whose use is not currently recommended. The power of an epidemiologic study to document a melanoma preventive effect is therefore severely compromised.

Melanoma is also characterized by a significant lag time between ultraviolet exposure and diagnosis of the malignancy. Hence it may be that use within the immediately prior 15 y bears no relation to melanoma risk even if sunscreens are remarkably effective in reducing risk over the longer term or when used in childhood and in the young adult years. Failure to take the lag period into account is a weakness in the analysis of many of these studies. The requirement for effective lotions to have been used many years prior to the study is a severe limitation on a study's power to detect an association that may be present.

THE CASE OF SQUAMOUS CELL CARCINOMA (SCC) OF THE SKIN

In light of these limitations, the association between sunscreen use and SCC bears scrutiny. The epidemiologic and clinical features of SCC

have left little doubt that sun exposure is a key cause of this malignancy. Furthermore, unlike melanoma, we have well-described mammalian models of ultraviolet radiation-induced SCC, and the action spectrum has been documented (de Gruijl *et al*, 1993; de Gruijl and van der Leun, 1994). This action spectrum is very similar to the erythema action spectrum in humans. Without a substantial difference between sunburn and SCC in action spectra, the compensation hypothesis cannot hold. Furthermore, intermittent patterns of exposure have not been linked to SCC risk, so inconsistant use of sunscreens is unlikely to be harmful for that reason. Sunscreens therefore should be effective in preventing SCC. Support for this inference is provided by two published randomized controlled trials that indicate that sunscreens are effective in the treatment and prevention of actinic keratoses, a documented precursor of SCC (Thompson *et al*, 1993; Naylor *et al*, 1995).

Two published observational studies have evaluated the link between SCC and sunscreen use. Both are cohort studies, so are free from some of the potential limitations of exposure measurement mentioned above, such as recall bias. The first of these found no significant association between SCC and sunscreen use (OR 0.9; 95% CI 0.6–1.2) (Grodstein *et al*, 1995). The second focussed primarily on actinic keratoses, and found no association between sunscreen use and either occurance of new actinic keratoses or regression of existing actinic keratoses (Harvey *et al*, 1996). Each study has its own limitations, but together they illustrate the difficulty of using current approaches for assessment of the impact of sunscreen use on the subsequent occurance of cutaneous malignancy.

CONCLUSIONS

Existing epidemiologic studies of the association of sunscreen use and melanoma risk are inadequate to determine the magnitude and direction of that association. A randomized trial of sunscreen use for the prevention of melanoma is not feasible because of the long lag period of melanoma, and because the incidence of melanoma, even in Queensland, Australia, which has the highest reported incidence, is only one per 3000 per year, so trial size and duration would be prohibitive. Also, performing random allocation while holding other sun protection measures constant is particularly difficult in a high incidence environment. Randomized trials of sunscreen use for surrogate endpoints (e.g., nevi) are possible and are underway.

Regrettably, it may be necessary to wait for another decade or two for adequate numbers of people to have been using high SPF broad spectrum sunscreens for long enough to have the power to evaluate the effectiveness of these lotions in epidemiologic studies of melanoma prevention. In the meanwhile, the use of sunscreens is justified by indirect evidence, including the known role of ultraviolet exposure in the genesis of melanomas, the likelihood that ultraviolet B is an important mediator of this process, and the direct evidence of the efficacy of sunscreens in the prevention of other forms of actinic neoplasia. As broader spectrum sunscreens become more widely used, the case for sunscreen use becomes more compelling, particularly when these lotions are used consistantly and for prevention of cancer (i.e., not for the purpose of prolonging sun exposure). The available evidence does not indicate a need to alter existing public health messages that encourage use of sunscreens, clothing, and sun avoidance for melanoma prevention.

Note: After acceptance of this paper, presentation of a randomized trial of sunscreen use among children suggested that sunscreen lotion is effective in preventing the formation of nevi (JK Rivers, March 1999).

The author is grateful to Drs Marianne Berwick and Adele Green for sharing their data. The author received support from grants AR43051 from the National Institutes of Health and from the Department of Veterans Affairs Cooperative Studies Program.

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